**UNITED STATES DISTRICT COURT**
**SOUTHERN DISTRICT OF NEW YORK**

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| **IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation**<br><br>**This Document Related To: All Cases** | **22md3043 (DLC)** |

**MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE TESTIMONY OF DR. STAN G. LOUIE**

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Because Defendants did not make Rule 702 objections expert by expert, they cannot keep their own arguments straight. Despite conceding in one brief, for example, that Dr. Stan Louie's role is "limited" to "address[ing] the level of exposure that purportedly can cause injury," Defs. ASD Br. at 47 n.119, Dkt. 1160, in a separate brief Defendants criticize him for misapplying studies *he never reviewed* to reach opinions he *never* rendered because they have nothing to do with the level of acetaminophen ("APAP") exposure that can cause injury, Defs. Mechanism Br. at 1-3, Dkt. 1165. Defendants' effort to exclude nonexistent testimony is an exercise in futility. The limited but important testimony Dr. Louie actually offers is based on his sound application of time-tested scientific methods. Aside from attacking their own strawmen, Defendants hardly say otherwise.

Dr. Louie is a Professor of Clinical Pharmacy. Plaintiffs engaged him to determine the dose and duration at which prenatal exposure to APAP increases the risk of developing ASD and ADHD. Dr. Louie opines that offspring of pregnant women who take therapeutic doses of APAP for at least 28 days have twice the risk of developing ASD or ADHD than pregnant women who do not. He further opines that the likely molecular mechanism through which APAP elevates that risk is oxidative stress in the brain, the result of depleted glutathione ("GSH") brought on by increased levels of NAPQI, a known and toxic metabolite of APAP. To reach these conclusions, Dr. Louie reviewed every relevant study, relying on his expertise in pharmacology, pharmacokinetics, and pharmacodynamics.

It is not "cherry picking," as Defendants claim, for an expert opining on the dose-response relationship to limit his review to studies that contained data on dose or duration of exposure. Defendants argue that Dr. Louie did not support his opinion that APAP can disrupt BDNF levels and cause the death of neurons, but his testimony makes clear that those possible disruptions would flow from the NAPQI pathway, not a separate mechanism.

Defendants' remaining arguments are a hodge-podge of baseless points. Defendants are wrong that Dr. Louie must show a consensus on the precise etiology of ASD and ADHD for a mechanism to be biologically *plausible*. Defendants are wrong that the peer-reviewed behavioral outcome studies on which Dr. Louie relies are less scientifically valid than studies using clinical diagnoses of ASD and ADHD (on which he also relies). Finally, Defendants are wrong that this Court can decide the merits on a motion concerning admissibility. Dr. Louie conducted a broad search of the relevant studies, excluded no study because of its results, and carefully weighed all the evidence to reach his conclusions. Because his methodology is sound, and his application of that methodology reasonable, his opinions are admissible.

## DR. LOUIE'S OPINIONS

### I. Assignment

Dr. Louie's assignment was "to determine, according to the publicly available evidence, the dose/duration at which prenatal (fetal) exposure to . . . acetaminophen . . . increases the risk of developing [ASD] and [ADHD]." Ex. 5, Louie Rep. at ¶ 15. As part of that assignment, Dr. Louie opined on the molecular mechanisms that could plausibly account for any increased risk. Ex. 5, Louie Rep. at ¶ 29.

Dr. Louie's assignment was consistent with his expertise in pharmacology, which studies "the safety and efficacy of drugs" like APAP at "therapeutic doses." Ex. 5, Louie Rep. at ¶ 4. As a Professor of Clinical Pharmacy at the University of Southern California, his research specifically encompasses not only "the implementation of clinical [drug] trials" but also more generally the "characterization of how a drug is absorbed in, distributed in, metabolized in, and eliminated from the body." Ex. 5, Louie Rep. at ¶ 1.

Dr. Louie is not an epidemiologist. Although Dr. Louie "routinely review[s], evaluate[s], and rel[ies] on epidemiological studies" as he did in his work in this case, he "examine[s] [that]

epidemiological data from the perspective of a pharmacologist, for example by using dosing/duration and other pharmacological data that exists in the epidemiological materials." Ex. 5, Louie Rep. at ¶ 33. He was not asked, therefore, and did not seek to perform a Bradford Hill or similar "general causation" analysis. Dr. Louie's opinions certainly support a causal relationship, but they concern the degree of exposure, the extent of the elevated risk, and the plausible mechanisms through which that risk is elevated.

## II. Methodology

Dr. Louie performed a literature search and medical literature evaluation, a fundamental and commonplace practice in pharmacology. Ex. 5, Louie Rep. at ¶¶ 17, 20. His searches were broad, using the terms "acetaminophen autism" and "acetaminophen ADHD" to generate the initial list of studies, and he narrowed that initial list only by adding such straightforward limiters as "epidemiological studies." Ex. 5, Louie Rep. at ¶ 20. He then reviewed all studies caught by his search as well as the studies cited therein.

Dr. Louie did not exclude any study from his search or review because it reached a particular result. He did assign greater weight to some studies over others, considering "1) population of the subjects analyzed, 2) number of participants, 3) study design in regard to statistical analysis, 4) pharmacologic data with regards to acetaminophen and/or its metabolites, and 5) post hoc biomarker analysis." "Studies correlating clinical outcome with drug exposure (e.g., intensity of dosage or duration of dosage) were given the highest priority" and additional preference was given to studies with a "large number of participants," Ex. 5, Louie Rep. ¶ 21, and those that he determined were "more methodologically sound, in particular those that adjusted for known confounders, mitigated bias from exposure and/or outcome misclassification or both." Ex. 5, Louie Rep. at ¶ 34.

Dr. Louie followed a similar procedure to analyze studies that concern the biologically

plausible mechanisms by which APAP increases the risk of ASD and ADHD. He used similar search terms to capture relevant studies and performed "a separate search between acetaminophen and glutathione in human subjects or animals." Ex. 5, Louie Rep. at ¶ 22. Once again, Dr. Louie did not exclude any study from his search or review because it reached a particular result. Weight was assigned to the studies based on "1) concentration or dosage of acetaminophen used in the therapeutic range for both humans or animal models, 2) . . . [the] evaluat[ion of] pharmacokinetics and biodistribution . . . [and] 3) [the use of] molecular biomarkers interrogating potential cause of neurodevelopmental changes." Ex. 5, Louie Rep. at ¶ 22.

The analyses Dr. Louie consulted for these literature reviews included human observational studies, behavioral outcome surveys, in vitro studies, and animal studies. He found no human clinical studies testing the effects of APAP exposure on pregnant women and their offspring, an unsurprising result given that they are ethically prohibited. In the absence of such studies, "the scientific community—and [pharmacology] in particular—recognizes the value and reliability of considering in vitro and animal studies." Ex. 5, Louie Rep. at ¶ 37. Animal studies are particularly valuable for dosing analysis because "allometric scaling" is an accepted method for calculating the human dose from the dose in animals. Ex. 10, Louie Reply Rep. at ¶ 27. The scientific community similarly recognizes validated, behavioral outcome surveys as accurate and reliable diagnostic tools. For example, the Ages and Stages Questionnaire (ASQ) used in Ex. 147, Brandlistuen (2013) met psychometric properties such as positive and negative predictive values (the ability of a test to determine if a patient actually has the disease or not) comparable to gold standard clinical assessments of developmental milestones during health checkups.[1]

## III. Dr. Louie's Analysis and Conclusions

[1] Ex. 165, Otalvaro (2018).

**A. Dr. Louie Finds Greatly Elevated Risk for Cumulative Exposure of 28 Days.**

Dr. Louie concluded that "[g]enerally, prenatal exposure to acetaminophen increases the risk of developing ASD and ADHD in offspring when acetaminophen is taken by the pregnant mother in the therapeutic dose range . . . for at least 28 cumulative days during pregnancy." Ex. 5, Louie Rep. at ¶ 28. Specifically, the risk increases "two-fold as compared to offspring with no exposure to acetaminophen." Ex. 5, Louie Rep. at ¶ 28.

In reaching this conclusion, Dr. Louie focused on the seven studies that examined data on days of exposure: Ystrom (2017), Gervin (2017), Gustavson (2021), Brandlistuen (2013), Liew (2014), Liew (2016), and Vlenterie (2016). Of these, he "assigned the greatest weight to Brandlistuen (2013) because it employed the strongest study design," including evaluation of same-sex siblings, "which allowed [the study authors] to adjust for familial and genetic factors." Ex. 5, Louie Rep. at ¶ 72. That study—which evaluated all pregnant Norwegian women and their offspring from 1999 to 2008, including 2,919 same-sex children pairs—showed "that offspring from pregnant mothers who took acetaminophen for more than 28 days were more likely to demonstrate neurodevelopmental outcomes at 3 years of age." Ex. 5, Louie Rep. at ¶ 73. The "offspring of mothers in the study who used ibuprofen during their pregnancy did not show poorer neurodevelopment." Ex. 5, Louie Rep. at ¶ 73.

These results were supported by Ystrom (2017), which found a "substantial[] associat[ion] with ADHD" in offspring whose mothers used APAP for more than 29 days during pregnancy, Ex. 5, Louie Rep. at ¶ 74; Liew (2014) and (2016), which found statistically significant increases in risk for, respectively, ADHD and ASD in offspring whose mothers used APAP for fewer than 28 days, Ex. 5, Louie Rep. at ¶ 77; and Gervin (2017), which found that "prenatal acetaminophen exposure for more than 20 days" was "associated with DNA methylation changes in cord blood, which was further correlated with clinical ADHD diagnoses," Ex. 5, Louie Rep. at ¶¶ 92, 176.

Indeed, several of these studies lent substantial support for an elevated risk resulting from fewer than 28 cumulative days of exposure.

Gustavson (2021) and Vlenterie (2016) also supported Dr. Louie's conclusions, although Dr. Louie assigned less weight to some of the results. Gustavson (2021), which Dr. Louie also credited as having a "strong study design," found a "two-fold increase in risk of ADHD diagnosis" for children "whose mothers used acetaminophen for 29 or more days during their pregnancy," Ex. 5, Louie Rep. at ¶ 78, but that association was no longer statistically significant when the authors controlled for potential genetic confounding by way of a sibling analysis.[2] Dr. Louie assigned virtually no weight to the sibling analysis because it was underpowered according to the study's own authors, using a sample size of only 34 out of the 26,613 children on which the study's results relied. Ex. 24, Louie Dep. Tr. at 119:12-120:1.[3]

Vlenterie (2016) similarly found that long-term exposure to acetaminophen during pregnancy "is associated with [an] increase in the risks of delayed motor milestone achievement and impaired communication skills" in offspring, Ex. 5, Louie Rep. at ¶ 80, but did not show a statistically significant association with other behavioral outcomes. Dr. Louie assigned less weight to Vlenterie because the study's own authors conceded that their propensity score-matched analysis failed to control for the severity of a number of indications including headaches, migraines, and infections, which could confound the results (or lack thereof).[4]

Dr. Louie also reviewed several studies not to determine what exposure elevates risk for ASD and ADHD but whether any elevation still occurs when controls are imposed for various biases and confounders. These studies—Ex. 46, Ji (2020) (ASD and ADHD), Ex. 71, Baker (2020)

[2] Ex. 52, Gustavson (2021).
[3] Ex. 81, Gustavson (2021) Appendix S2 § 2.3, 7:18-19 ("These numbers show that statistical power to detect within effects was relatively low. Hence, these results should be interpreted with caution.").
[4] *See* Ex. 108, Vlenterie (2016) at 2006.

(ADHD), Ex. 142, Anand (2021) (ADHD), and Ex. 37, Alemany (2021) (ASD and ADHD)—did not examine or report dose and exposure data, but they "corroborate the findings of the studies . . . that assess exposure duration." Ex. 5, Louie Rep. at ¶ 84. For example, Ex. 46, Ji (2020), Ex. 71, Baker (2020), and Ex. 142, Anand (2021) all used placental and fetal biomarkers (cord blood and meconium) to assess in utero APAP exposure and physician diagnoses and neuroimaging to assess ASD and ADHD outcomes. Elevations in risk are remarkably consistent among Ji (2020), Baker (2020), Anand (2021), and other epidemiological studies based on maternal reporting of in utero APAP exposure and ASD and ADHD outcomes. Dr. Louie noted this consistency increases his confidence that the epidemiological studies based on maternal reporting are not biased by exposure or outcome misclassification. *See* Ex. 5, Louie Rep. at ¶¶ 34, 83, and 96.

**B. Dr. Louie Finds This Risk Is Plausibly Elevated Through Increased Oxidative Stress.**

Dr. Louie concludes a plausible reason for the "increased risk" of both ASD and ADHD "is that (i) acetaminophen and its metabolites can deplete glutathione (GSH), thereby causing oxidative stress systemically and in the brain, and (ii) a particular acetaminophen metabolite, NAPQI, and its adducts can induce oxidative stress, immune reactivity, and inflammation." Ex. 5, Louie Rep. at ¶ 29. Dr. Louie again reviewed "data, information, and studies concerning mechanism of action in [his] role as a clinical pharmacologist, drug development expert, and translational scientist." Ex. 5, Louie Rep. at ¶ 100.

Dr. Louie first identified oxidative stress as a possible molecular pathway for APAP to cause ASD and ADHD. Both ASD and ADHD, as well as other neurodevelopmental disorders, potentially result from oxidative stress in the brain. Ex. 5, Louie Rep. at ¶¶ 28-29. Oxidative stress—the cellular damage that can result from reactive oxygen intermediaries binding to healthy cells—is mitigated by various naturally produced antioxidants, including GSH. Ex. 5, Louie Rep.

at ¶ 109. NAPQI is both such a reactive oxygen intermediary and a "well-understood reactive and toxic metabolite of acetaminophen." Ex. 5, Louie Rep. at ¶ 105. NAPQI is "rapidly detoxified through chemical interaction with GSH," Ex. 5, Louie Rep. at ¶ 105, but "at high systemic acetaminophen concentrations . . . the body's endogenous levels of GSH are reduced and, as a consequence, may become unable to accommodate the excess NAPQI levels that are produced," Ex. 5, Louie Rep. at ¶ 105.

Dr. Louie then reviewed a variety of relevant studies assessing the plausibility of the various steps in this process. His review included studies concerning whether:

- NAPQI levels were elevated in pregnant women taking acetaminophen (Mian (2020)), Louie Rep. at ¶ 107;
- NAPQI can get through the blood-brain barrier (Posadas (2010), Kumpulainen (2007)), Louie Rep. at ¶¶ 106, 153;
- Lower GSH levels in pregnant women correlate with low GSH levels in fetuses (Kuster (2011), Miranda-Guisado (2012)), Louie Rep. at ¶¶ 111-17;
- GSH depletion correlates with oxidative stress (Vaziri (2000)), Louie Rep. at ¶¶ 118-19;
- Therapeutic doses of acetaminophen correlate with GSH depletion (Nuttall (2003), Dimova (2005)), Louie Rep. at ¶¶ 126-32;
- Acetaminophen exposure to pregnant women correlates with exposure in fetuses (Levy (1975), Forrest (1982), Nitsche (2017)), Louie Rep. at ¶¶ 141-42, 146; and
- Depleted GSH and acetaminophen in fetuses and children correlate with an elevated risk of ASD or ADHD (Nasim (2019), Anand (2021)), Louie Rep. at ¶ 123-24, 162-64.

From this extensive array of sources, Dr. Louie found support for the plausible pathway at every step. Dr. Louie did not exclude or ignore relevant studies, but he did assign different weights across studies and within study results. Ex. 5, Louie Rep. at ¶¶ 129-130, 136.

In the course of his review, Dr. Louie found additional support for alternative molecular pathways through which APAP might elevate the risk of ASD and ADHD, including acetaminophen-induced alteration of gene expression that is associated with neurodevelopmental

disorders. Ex. 5, Louie Rep. at ¶¶ 168-85. Although he identified three persuasive studies supportive of such a mechanism (Eslamimehr (2018), Gervin (2017), Carter (2016)), he did not review sufficient data to draw a definitive conclusion.

## ARGUMENT[5]

### I. Dr. Louie Offers Reliable Testimony Regarding the Prenatal Exposure at Which APAP Increases the Risk of ASD and ADHD.

#### A. Many of Defendants' Arguments Fundamentally Misconceive Dr. Louie's Opinions.

Defendants argue that "Dr. Baccarelli, Cabrera, Hollander and Louie" (1) cherry pick studies supporting association and ignore those supporting no association, and (2) fail to account for significant limitations in the study on which they rely. Defs. ASD Br. at 58; Defs. ADHD Br. at 41, Dkt. 1162. Defendants also argue that (3) Dr. Louie fails to "stratify usage" of APAP beyond 28 days or offer any opinions regarding how distribution of those 28 days impacts risk. Defs. ASD Br. at 72; Defs. ADHD Br. at 17. These arguments fundamentally misapprehend the nature of Dr. Louie's engagement.

1. *Dr. Louie Did Not Cherry Pick Studies.*

"An expert must not cherry-pick from the scientific landscape and present the Court with what he believes the final picture looks like." *Daniels-Feasel v. Forest Pharm., Inc.*, No. 17-cv-4188, 2021 WL 4037820, at *4 (S.D.N.Y. Sept. 3, 2021) (internal quotation marks omitted). But "[d]ifferences of opinion about what is important among evidentiary facts go to the weight of the expert's opinion, not an expert's ability to offer that opinion." *Pearlstein v. Blackberry Ltd.*, No. 13-cv-7060, 2021 WL 4131646, at *9 (S.D.N.Y. Sept. 10, 2021) (holding that expert's conclusion that certain facts were not important did not constitute cherry picking).

Defendants fault Dr. Louie for not evaluating Ji (2018), Saunders (2019), and Hornig

[5] Plaintiffs refer the Court to the Rule 702 legal standard set forth in Plaintiffs' Baccarelli Opposition at 33–34.

(2018). Defs. ASD Br. at 52 n.128. But Dr. Louie did not consider those studies because they do not analyze or report exposure data, which is plainly necessary for an expert opining on the dose.[6] *See Pearlstein*, 2021 WL 4131646, at *9. Dr. Louie found seven studies that did analyze exposure data—Ystrom (2017), Gervin (2017), Gustavson (2021), Brandlistuen (2013), Liew (2014), Liew (2016), and Vlenterie (2016), Ex. 5, Louie Rep. at ¶ 69—and he considered each one. Dr. Louie also considered additional epidemiological studies for the limited purpose of ensuring that the seven primary studies he relied upon were not biased "due to exposure and outcome misclassification." Ex. 5, Louie Rep. at ¶ 83. All studies with direct biomarkers were considered for this limited purpose. Ji (2018), Saunders (2019), and Hornig (2018) were not considered because none of them used placental and fetal biomarkers (cord blood and meconium). While Ji (2018) used *maternal* biomarkers, the same research group subsequently published Ji (2020) which used placental biomarkers, Defs. ASD Br., at 9-11, a superior, more direct, and more relevant measure of in utero APAP exposure, on which Dr. Louie did rely. Ex. 5, Louie Rep. at ¶¶ 83-85.

Defendants also argue that Dr. Louie adopts "only the less rigorous half of" Gustavson (2021), purportedly "ignor[ing] the sibling-control results" because "they do not support plaintiffs' causation theory." Defs. ADHD Br. at 28. But, as Dr. Louie explained at his deposition, he assigned virtually no weight to the sibling-control results because they were underpowered, using a sample size of only 34 out of the 26,613 children on which the study's results relied. Ex. 24, Louie Dep. Tr. at 119:12-120:1.[7] Consistent with being based on too small a sample size, the control group did not suggest a negative association, but merely produced inconclusive results.[8]

[6] *See* Ex. 66, Ji (2018); Ex. 81, Hornig (2018).
[7] *Compare* Ex. 52, Gustavson (2021) at 1; Ex. 81, Gustavson (2021) Appendix S2 § 2.3, 7:9-19.
[8] Ex. 81, Gustavson (2021) Appendix S2 § 2.3, 7:9-19. *See also* Baccarelli Opp'n at 16–17.

2. *Dr. Louie Did Not Fail to Account for Study Limitations.*

"[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study." *Daniels-Feasel*, 2021 WL 4037820, at *4. But an expert's omission of a variable in her analysis goes to the weight of the expert's testimony, not its admissibility. *See Laureano v. City of New York*, No. 17-cv-181, 2021 WL 3272002, at *4 (S.D.N.Y. July 30, 2021) ("[F]ailure to account for [an] unknown variable . . . affect[s] the weight [of expert testimony] rather than its admissibility."); *Freeland v. AT & T Corp.*, 238 F.R.D. 130, 145 (S.D.N.Y. 2006) (holding that analysis is admissible when it accounts for major factors but not all measurable variables).

Again lumping Dr. Louie with Drs. Baccarelli, Cabrera, and Hollander, Defendants argue that Dr. Louie ignores limitations in the studies on which he relies. Defs. ASD Br. at 27; Defs. ADHD Br. at 19. According to Defendants, it is a "critical flaw" for Dr. Louie to rely on Ji (2020) because its authors limit the study's applicability to "maternal use of acetaminophen during peripartum period" when he is opining on "prenatal exposure to acetaminophen." Defs. ASD Br. at 28. Defendants also criticize Dr. Louie and his fellow experts for reliance on Ji (2020), Baker (2020), and Liew (2014) because the studies' authors were "unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors." Defs. ASD Br. at 29; *see also* Defs. ADHD Br. at 21 (Baker (2020) authors acknowledged the possibility of "confounding by unknown genetic, social, and other familial factors").

For Ji (2020) and Baker (2020), Defendants' critique misses the mark entirely. Dr. Louie did not rely on either for its exposure data because *neither* reports exposure data. *See Pearlstein*, 2021 WL 4131646, at *9. And it makes no sense to criticize Dr. Louie's reliance on Ji (2020) and Baker (2020) for failing to account for "unknown" or "unmeasured" residual genetic or other confounders when he expressly relied on them to confirm the absence of "confounding by

indication and other *known* confounders." Ex. 5, Louie Rep. at ¶ 83 (emphasis added).

As for Dr. Louie's reliance on Liew (2014) and Liew (2016), one of the strengths of Dr. Louie's opinion is the diversity of studies on which he relies. An individual study cannot control for all variables, and it certainly cannot control for "unknown" variables. *Laureano*, 2021 WL 3272002, at *4; *Freeland*, 238 F.R.D. 130 at 145. But the fact that Dr. Louie consistently saw an elevated risk for ASD and ADHD across a substantial set of studies that collectively controlled for a large number of biases and confounding variables considerably reduces the possibility of an erroneous association.[9] *See Daniels-Feasel*, 2021 WL 4037820, at *9 (noting that research becomes more convincing when replicated using different research methods and designs).

3. *Dr. Louie's Opinions Are No Less Reliable or Relevant Because He Did Not Stratify or Otherwise Opine on the Distribution of Exposure.*

Defendants provide no authority for why any of Dr. Louie's opinions should be excluded because he does not provide a detailed risk-exposure *distribution* as opposed to a *cut-off*. Defendants ominously write that Dr. Louie "lumped women with widely varying exposures together in the 29+ days category," but so what? Any attempt at line drawing is going to lump together individuals who barely cross the line with those who are well beyond it. There is nothing "unscientific and unreliable" about that. Defs. ASD Br. at 71-72. Contrary to Defendants' claim that Dr. Louie's 28-day threshold for risk elevation was "arbitrary" or pulled from "thin air," Dr. Louie selected 28 days because it was the *longest*—and thus most *Defendant* friendly—period the relevant studies supported.[10] Defs. ASD Br. at 2, 74. As Dr. Louie notes on multiple occasions in his report, there was ample evidence in the studies he reviewed for a lower threshold. Ystrom (2017), Liew (2014), and Liew (2016) all found statistically significant elevations in risk of ASD

[9] Ex. 5, Louie Rep. at ¶ 33 & n.5. *See also* Baccarelli Opp'n at 10-17.
[10] *See* Ex. 147, Brandlistuen (2013); Ex. 85, Ystrom (2017); Ex. 52, Gustavson (2021) (non-sibling analysis with larger sample size and greater statistical power); and, to a lesser extent, Ex. 108, Vlenterie (2016).

and ADHD in as little as one week of in utero acetaminophen exposure in certain populations. Ex. 5, Louie Rep. at ¶¶ 76-78.

**B. Dr. Louie Reasonably Relied on Surveys of Behavioral Outcomes.**

Defendants criticize "so-called 'proxy' studies that use various screening tools and questionnaires that measure, *inter alia*, behavior, cognition, temperament, psychomotor development, IQ and attention," arguing that they cannot serve as a "reliable basis" for Dr. Louie's opinions. Defs. ASD Br. at 38. Defendants are simply wrong to cast behavioral outcome studies as unreliable. Plaintiffs incorporate by reference their oppositions to the motions to exclude Drs. Baccarelli and Hollander, which rebut Defendants' wholesale disregard of these studies.

## II. Dr. Louie Reliably Identifies a Plausible Mechanism Through Which APAP Increases the Risk of ASD and ADHD.

**A. Defendants Are Wrong on the Applicable Legal and Scientific Standards.**

Defendants argue that Dr. Louie's (and other plaintiff experts') opinions regarding biological plausibility are inadmissible because (1) "[i]dentifying the process by which ASD or ADHD occurs is still beyond the ability of medical science," Defs. Mechanism Br. at 14, and (2) Dr. Louie fails "to distinguish between ASD and ADHD," Defs. Mechanism Br. at 16. Both arguments confuse the applicable law and science.[11]

*1. The Law Does Not Require Scientific Certainty on the Etiology of ASD and ADHD.*

Plausible means "possible" or "credible," not certain.[12] Defendants sometimes accept this black-letter point. Defs. Mechanism Br. at 1. But more often, they insist that a biologically plausible mechanisms only counts if it is conclusively established. *Id*. at 12-14.

[11] Without citing Dr. Louie, Defendants argue generally that "plaintiffs' expert opinions are also unreliable because they fail to justify extrapolating from findings in rodents . . . to humans." Defs. Mechanism Br. at 14. To the extent Defendants are directing this critique to Dr. Louie's specifically, it is baseless. Dr. Louie explains in numerous places why it is proper to extrapolate from rodents to humans. Ex. 5, Louie Rep. at ¶¶ 37, 101, 102. *See also* Cabrea Opp'n at 5–6; 22–24.

[12] Ex. 69, Hill (1965), at 296-98; Ex. 163, Oleckno (2008), at 187-89; Ex. 168, Rothman (2008), at 30-31; *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 22, 25 (1st Cir. 2011).

Dr. Louie opined about a biologically plausible mechanism, not a certain one. That framework follows the law in this Circuit. *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d at 183; *see also In re Pfizer Inc. Secs. Litig.*, Nos. 04-cv-9866, 05-md-1688, 2010 WL 1047618 at *6 (S.D.N.Y. Mar. 22, 2010) (allowing expert mechanism testimony where "deemed plausible and credible in the relevant medical literature" and notwithstanding that the "mechanism [had not been] not proven conclusively or uniformly accepted").[13] Other courts have reached the same conclusion.[14]

Dr. Louie's opinion meets the standard. Dr. Louie describes and supports with evidence every step in the causal chain, Ex. 5, Louie Rep. at ¶ 29, including: (1) how APAP is absorbed, distributed, and metabolized through the body, *id.* at ¶ 104; (2) how one of its metabolites—NAPQI—can make it through the blood-brain-barrier to interact with brain tissue, *id.* at ¶ 106; (3) how sufficient levels of NAPQI can deplete GSH levels, *id.* at ¶ 132; (4) how GSH depletion can cause oxidative stress, *id.* at ¶ 136; and (5) how oxidative stress in brain tissue is associated with neurodevelopmental disorders like ASD and ADHD, *id.* at ¶ 155-67. All of these steps are recognized in peer-reviewed literature.[15] There is little doubt regarding the plausibility of each part and the whole to which they sum.

The cases Defendants cite to argue the contrary are inapposite. In stark contrast to Dr.

[13] *Deutsch v. Novartis Pharms. Corp.*, 768 F. Supp. 2d 420, 438 (E.D.N.Y. 2011) ("That the mechanism remains unknown does not mean that the one proposed by the [plaintiffs' experts] is not widely accepted as plausible."); *Drake v. Allergan, Inc*., No. 13-cv-234, 2014 WL 5392995, at *7 (D. Vt. 2014) ("[I]t is not necessary for an expert to know the exact mechanism of how a drug causes an injury in order for her opinion on causation to be reliable and admissible.").

[14] *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 25 (1st Cir. 2011); *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1236-37 (9th Cir. 2017); *In re Abilify (Ariprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018); *In re PPA Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003); *Wagoner v. Exxon Mobil Corp*., 813 F. Supp. 2d 771 (E.D. La. 2011); *In re Avandia Mktg., Sales Pracs. & Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9 (E.D. Pa. Jan. 4, 2011).

[15] *See, e.g.*, Ex. 5, Louie Rep. at ¶¶ 104 n.68, 105-06 nn. 69-72, 115 & n.79, 123 & n.82 (discussing such peer-reviewed studies).

Louie's involved discussion regarding specific biological pathways underlying ASD and ADHD, the expert excluded by the court in *In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, was entirely "silen[t]" on "the basic operation of the 'mechanism' and 'pathway'" that were posited to link the drug at issue to the condition it allegedly caused. 341 F. Supp. 3d 213, 285 (S.D.N.Y. 2018), *aff'd* 982 F.3d 113 (2d Cir. 2020). And in *In re Accutane Prods. Liab*., the expert conceded that none of the possible mechanisms he proposed had even been tested, whereas Dr. Louie's opinions are based upon his review of numerous studies testing aspects of the underlying mechanisms that he posits as a link between APAP and ASD and ADHD. 511 F. Supp. 2d 1288, 1296 (M.D. Fla. 2007). The robust medical literature relied upon by Dr. Louie also sets him apart from the expert excluded in *Hendrix ex rel. G.P. v. Evenflo Co*., who failed to present any medical literature that even mentioned or purported to show the physiological process by which a brain injury could result in ASD, leading the district court to conclude that *none* of the cited literature supported his proffered physiological process. 609 F.3d 1183, 1199-1201 (11th Cir. 2010). Defendants also fail to acknowledge that the scientific understanding of ASD and ADHD and their causal factors has improved considerably since *Hendrix* was decided in 2010.

2. *Defendants Are Both Wrong and Confused Regarding Dr. Louie's Alleged Conflation of ASD and ADHD in His Analysis.*

Defendants characterize Dr. Louie as "believ[ing] [that] ASD and ADHD . . . arise from a single cause." Defs. Mechanism Br. at 17. Nowhere in Dr. Louie's reports or deposition does Dr. Louie express that view, and Defendants do not provide a citation supporting that characterization. Dr. Louie agrees with his fellow experts and the scientific consensus that most presentations of ASD and ADHD have multiple causes. Dr. Louie acknowledges that genetics can influence ASD and ADHD risk, as well as individual susceptibility to environmental exposures such as in utero APAP exposure. Ex. 5, Louie Rep. at ¶¶ 30, 72, 76-78 ("[I]t is important to note that human beings

can vary in their individual susceptibility to acetaminophen, which may include differences as to how acetaminophen is metabolized and eliminated."). Defendants also suggest that Dr. Louie provides no more detail beyond "therapeutic doses of acetaminophen can affect brain development." Defs. Mechanism Br. at 16. While that statement by Dr. Louie is true (and unchallenged by Defendants), it ignores dozens of pages in Dr. Louie's report where he not only explains precisely what molecular changes APAP induces in the brain, Ex. 5, Louie Rep. at ¶¶ 103-10, but also delineates where he connects those molecular changes to ASD and ADHD, Ex. 5, Louie Rep. at ¶¶ 155-85.

Defendants also miss the larger point: it should come as no surprise that Dr. Louie and his fellow experts identify the likely mechanisms for APAP to elevate the risk of ASD as the same as those for ADHD. Unlike the precise etiology of ASD and ADHD, there *is* scientific consensus that ASD and ADHD have a shared pathophysiology, overlapping biological pathways, and shared causal factors.[16] Consistent with that consensus, Dr. Louie explained how APAP can cause oxidative stress in the brain, and provided evidence showing that depleted GSH and oxidative stress are associated with ADHD. Ex. 5, Louie Rep. at ⁋⁋ 123-24 (discussing Nasim (2019), which found "a reduction in GSH levels and antioxidant components . . . in individuals with ADHD"); Ex. 5, Louie Rep. at ⁋⁋ 162-64 (discussing Anand (2021), which found an "inability to neutralize oxidative stress" in participants that were "two-fold more likely to develop ADHD").The two out-of-circuit cases that Defendants cite in support of their argument are not to the contrary, for the reasons stated in Plaintiffs' Opposition to the Motion to Exclude Dr. Hollander.

**B. Dr. Louie's Opinions Regarding Oxidative Stress Are Reliable.**

Defendants also argue that Dr. Louie's opinions regarding the oxidative stress mechanism

[16] Ex. 93, Faraone (2021).

are unreliable because he: (1) "ignored the mechanistic results" of Klein (2020), Defs. Mechanism Br. at 22; (2) "improperly rel[ied] on studies that did not involve brains at all, without offering a scientific basis to extrapolate from other organs, fluids, or cells," *id.* at 25; and (3) relied on "studies that show an association between GSH levels or oxidative stress and ASD or ADHD post-birth," *id.* at 27. None of these arguments has merit.

First, Dr. Louie did not review Klein (2020) because the relevant information from that study was contained in and cited by Rigobello (2021), which he did review. Both Klein (2020) and Rigobello (2021) examine behavioral issues—which the Klein (2020) authors recognize as "relevant to neurodevelopmental disorders such as ASD and ADHD"[17]—and brain GSH levels in the offspring of pregnant rats exposed to subtoxic doses of acetaminophen.[18] Klein (2020) found behavioral perturbations consistent with acetaminophen as a "developmental neurotoxicant," but did not find reduced GSH in certain regions of the brain, whereas Rigobello (2021) found "increases in fetal brain oxidative stress corresponding with poorer neurological development parameters in the offspring."[19] Importantly, Rigobello (2021) explicitly updated Klein's (2020) methodology, using a more sensitive detection of GSH and evaluating more brain regions in comparison.[20] It was entirely expected, therefore, for Rigobello (2021) to detect a statistically significant association when Klein (2020) did not, and entirely reasonable for Dr. Louie to rely on Rigobello (2021) but not Klein (2020).[21]

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[17] Ex. 143, Klein (2020) at 1.
[18] Ex. 143, Klein (2020) at 1; Ex. 167, Rigobello (2021) at 1.
[19] Ex. 10, Reply Rep. at ¶ 23. *See also* Ex. 143, Klein (2020) at 1, 6, 7 (cited at Ex. 167, Rigobello (2021), at 2); Ex. 167, Rigobello (2021) at 4.
[20] Rigobello (2021) additionally explicitly updated Klein (2020)'s methodology with "further modifications." *Compare* Ex. 167, Rigobello (2021) at 3, *with* Ex.143, Klein (2020) at 3.
[21] Defendants also criticize Dr. Louie's reliance on Rigobello 2021 because he "mention[s] the single positive result and ignore[es] the negative ones." Defs. Mechanism Br. at 23. When, as in Rigobello 2021, sample size is low and the analysis is underpowered, null results are to be expected. The result on which Dr. Louie relies is therefore even more likely to be true because it was statistically significant notwithstanding this expectation.

Second, Defendants' criticism of Dr. Louie's reliance on studies that "did not involve brains" goes to the weight of Dr. Louie's testimony, not its admissibility. Dr. Louie did consider whether studies of liver tissue would provide the same insights as those of brain tissue, Ex. 5, Louie Rep. at ¶ 160, and provided evidence that brain and blood serum levels of acetaminophen were consistent, *id.* at ¶¶ 148-50. Defendants' theories to the contrary, Defs. Mechanism Br. at 26, are for a jury to evaluate. *See In re Pfizer Inc. Secs. Litig.*, 2010 WL 1047618 at *7; *In re Fosamax Prods. Liab. Litigation*, 645 F. Supp. 2d at 178.

Third, it similarly goes to the weight of Dr. Louie's testimony whether high levels of oxidative stress in children diagnosed with ASD are evidence of ASD elevating those levels rather than oxidative stress causing ASD. It is well-understood that oxidative stress can induce a positive feedback loop, with oxidative stress first causing neuronal injury/death, which then further increases oxidative stress.[22] Accordingly, the fact that ASD can cause oxidative stress does not undermine the plausible conclusion that oxidative stress causes ASD, especially when Dr. Louie presents evidence not only of oxidative stress post-onset of neurobehavioral symptoms but also pre-onset. *See Laureano*, 2021 WL 3272002, at *4 ("[A]s long as an expert's scientific testimony rests on good grounds, based on what is known, it should be tested by the adversarial process—competing expert testimony and active cross-examination—rather than excluded from jurors for fear they will not grasp its complexities or satisfactorily weigh its inadequacies.").

**C. Dr. Louie Does Not Draw Conclusions Regarding Other Potential Mechanisms.**

Dr. Louie offers limited opinions regarding certain epigenetic studies suggesting the possibility of an alternative mechanism, namely, APAP inducement of DNA methylation, which in turn alters the expression of certain genes linked to ASD and ADHD. Ex. 5, Louie Rep. at ¶¶ 67-

[22] *See, e.g.*, Ex. 145, Shirley (2014) at 476.

72. But as he makes clear, Ex. 5, Louie Rep. at ¶ 9, Dr. Louie does not intend to testify that DNA methylation is a plausible mechanism for acetaminophen elevating the risk of ASD and ADHD, only that the studies he cites are largely supportive of that thesis.[23] Defendants nevertheless argue that even these opinions should be excluded because Dr. Louie purportedly "rel[ies] on cherry-picked literature" that lacks evidence that the described "epigenetic changes . . . could lead to the development of ASD or ADHD." Defs. Mechanism Br. at 32-33. Defendants specifically point to Dr. Louie's failure to consider Olstad (2023). *Id.* at 32.

However, Dr. Louie did address Olstad (2023) in his rebuttal report, distinguishing the technology used in Olstad (2023) from that used in Gervin (2017) as a reasonable basis for the authors' inability to replicate certain findings between the studies. Ex. 10, Reply Rep. at ¶¶ 43-44. Moreover, the fact that Olstad (2023) "employed a different technology for detecting DNA methylation differences" than the one used by Gervin (2017) "may explain the differences in the outcomes." Ex. 10, Reply Rep. at ¶ 44. Importantly, the technology used in Gervin (2017) specifically targets CpG islands, which regulate the expression of genes such as those implicated in ADHD at a much higher rate than CpG sites across the rest of the genome.[24]

Defendants also argue that Dr. Louie's reliance on Eslamimehr (2022) and Addo (2019) is improper because "none of the studies . . . tested cells in the brain." Defs. Mechanism Br. at 34. Taking biopsies of brain samples would be highly invasive and unethical. Eslamimehr (2022) examined cord blood and Addo (2019) examined placental tissue, some of the best samples outside

[23] Defendants also argue that Dr. Louie's purported theories concerning BDNF levels and neuronal death should also be excluded as "barely formed opinions." Defs. Mechanism Br. at 6. Defendants mistake Dr. Louie's citation to Viberg 2014 and Posadas 2010 as attempts to express opinions on a separate molecular mechanism when they are in fact cited in support of Dr. Louie's opinion concerning GSH depletion and oxidative stress. Ex. 5, Louie Rep. at ¶¶ 147, 151 (offering Viberg (2014) as an example of studies which "Demonstrate[] That Therapeutic Dosages of Acetaminophen Can Affect Brain Development"); *id.* at ¶¶ 106, 154 (connecting Posadas (2010) to neurodevelopment). Dr. Louie offers no opinions on mechanism beyond GSH depletion and DNA methylation.
[24] *See, e.g.*, Ex. 158, Lim (2019).

the brain. Ex. 5, Louie Rep. at ¶¶ 174-75; Ex. 10 Reply Rep. at ¶ 43; Ex. 146, Addo (2019) at 1. Reliance on the best evidence available cannot be a basis to exclude testimony.

**CONCLUSION**

For the reasons set forth above, Defendants motions to exclude the testimony of Dr. Stan Louie should be denied.

Dated: October 10, 2023

Respectfully submitted,

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